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Network Meta-analysis and Pharmacoeconomic Evaluation of Fluconazole, Itraconazole, Posaconazole, and Voriconazole in Invasive Fungal Infection Prophylaxis

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Invasive fungal infections (IFIs) are associated with high mortality rates and large economic burdens. Triazole prophylaxis is used for at-risk patients with hematological malignancies or stem cell transplants. We evaluated both the efficacy and the cost-effectiveness of triazole prophylaxis. A network meta-analysis (NMA) of randomized controlled trials (RCTs) evaluating fluconazole, itraconazole capsule and solution, posaconazole, and voriconazole was conducted. The outcomes of interest included the incidences of IFIs and deaths. This was coupled with a cost-effectiveness analysis from patient perspective over a lifetime horizon. Probabilities of transitions between health states were derived from the NMA. Resource use and costs were obtained from the Singapore health care institution. Data on 5,505 participants in 21 RCTs were included. Other than itraconazole capsule, all triazole antifungals were effective in reducing IFIs. Posaconazole was better than fluconazole (odds ratio [OR], 0.35 [95% confidence interval [CI], 0.16 to 0.73]) and itraconazole capsule (OR, 0.25 [95% CI, 0.06 to 0.97]), but not voriconazole (OR, 1.31 [95% CI, 0.43 to 4.01]), in preventing IFIs. Posaconazole significantly reduced all-cause deaths, compared to placebo, fluconazole, and itraconazole solution (OR, 0.49 to 0.54 [95% CI, 0.28 to 0.88]). The incremental cost-effectiveness ratio for itraconazole solution was lower than that for posaconazole (Singapore dollars [SGD] 12,546 versus SGD 26,817 per IFI avoided and SGD 5,844 versus SGD 12,423 per LY saved) for transplant patients. For leukemia patients, itraconazole solution was the dominant strategy. Voriconazole was dominated by posaconazole. All triazole antifungals except itraconazole capsule were effective in preventing IFIs. Posaconazole was more efficacious in reducing IFIs and all-cause deaths than were fluconazole and itraconazole. Both itraconazole solution and posaconazole were cost-effective in the Singapore health care setting.

Invasive fungal infections (IFIs) are a leading cause of morbidity and death in immunocompromised patients. The management and prevention of IFIs require substantial expenditures and are significant health care burdens. Patients with hematological malignancies, such as acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), who are undergoing chemotherapy or hematopoietic stem cell transplantation (HSCT) are at high risk of developing IFIs (1, 2). *Candida* and *Aspergillus* are the most common fungi causing IFIs (3). Prophylactic strategies are central to the containment of IFIs (4, 5), because early diagnosis of disease, which is critical for optimizing treatment outcomes, remains elusive despite recent advances in diagnostic techniques (6).

Triazole, polyene, and echinocandin antifungal agents have been employed in prophylactic strategies against IFIs. Antifungal prophylaxis has significantly reduced the incidence of IFIs and, notably, the triazole antifungals have had positive effects on IFI-related mortality rates. Narrow-spectrum triazoles such as fluconazole and itraconazole have seen broad usage in patients over the years; however, they are limited by their antifungal spectra and the development of breakthrough infections (7). Newer triazoles such as voriconazole and posaconazole, while exhibiting favorable pharmacological profiles and extended activity spectra, are more costly. In settings in which health care resources are not infinite, the question of affordability to the patient and to the health care system is critical. Previous pharmacoeconomic studies of antifungal prophylaxis were limited in the range of comparisons between the various agents (8–10). This may be attributable to the nature of the data employed in the analyses, that is, randomized controlled trials (RCTs) and cohort studies. For instance, the pharmacoeconomic evaluation of posaconazole was based exclusively on two pivotal clinical studies (11, 12), which limited the comparator to fluconazole (9). Two other studies attempted to determine the comparative cost-effectiveness of posaconazole, voriconazole, and fluconazole using patient-level data (8, 13).

The objective of this study was to examine the efficacy, tolerability, and cost-effectiveness of triazole antifungal prophylaxis for patients with hematological malignancies who were undergoing

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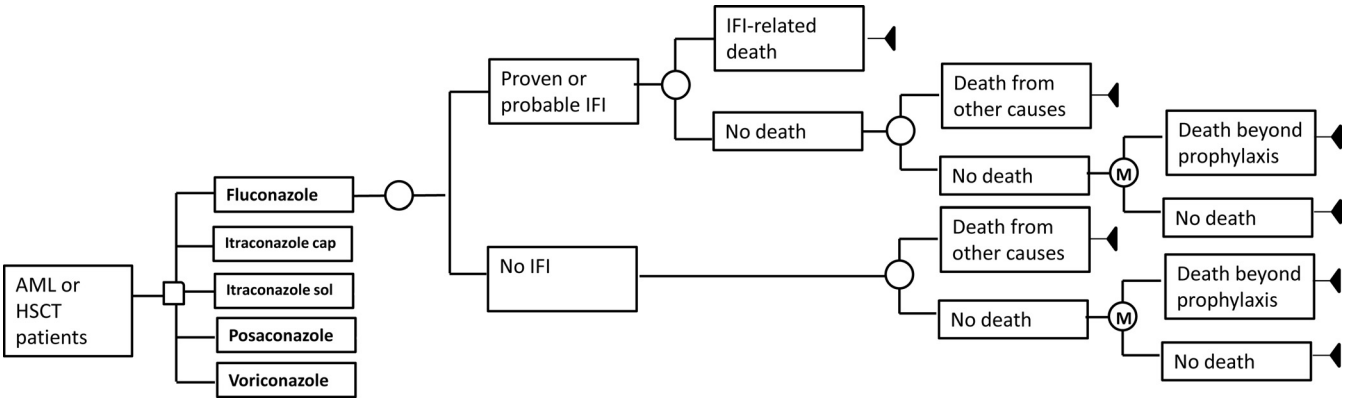


FIG 1 Schematic representation of the cost-effectiveness analysis model. AML, acute myeloid leukemia; HSCT, hematopoietic stem cell; cap, capsule; sol, solution; IFI, invasive fungal infection; M, Markov model.

chemotherapy or HSCT. We designed a network meta-analysis (NMA) to evaluate the comparative efficacy of all triazole antifungals on the market, namely, fluconazole, itraconazole (capsule and solution), posaconazole, and voriconazole. The simultaneous analysis of direct evidence (when there were head-to-head trials between comparator drugs) and indirect evidence (when there was a common treatment connecting the comparator drugs of interest) made provision for comparisons even when no clinical studies between some of the agents existed. By using clinical efficacy data generated from the network meta-analysis, data on local health care resource use, and epidemiological data, a model-based pharmacoeconomic analysis was conceived. Such an analysis of efficacy and cost-effectiveness for the prophylaxis of IFIs, incorporating all commercially available triazole antifungals, has not been attempted previously.

MATERIALS AND METHODS

Systematic search and study selection. A systematic search of PubMed and the Cochrane Library was conducted up to November 2014. The Cochrane highly sensitive search strategy was used to identify relevant randomized controlled trials (RCTs) (14) evaluating triazole antifungals for prophylaxis. The following medical subject heading (MeSH) terms and text words, in various combinations, were included: prophylaxis, prevention, antifungal agents, triazole, fluconazole, itraconazole, posaconazole, and voriconazole (see Tables S1 and S2 in the supplemental material).

Study selection was performed by two reviewers (Y.J.Z. and G.T.), and disagreements were resolved through consensus. We included RCTs that evaluated one triazole against another or against placebo as prophylaxis against IFIs. The participants were adult patients with hematological malignancies who were undergoing chemotherapy or HSCT. We excluded trials that exclusively studied patients with graft-versus-host disease (GVHD) or patients who had undergone multiple cycles of chemotherapy. Such patients have different risks of IFIs than our primary population of interest, and inclusion of such studies might have increased the heterogeneity of the evidence network. We included only articles published in English-language journals.

The outcomes of interest were overall incidence of proven or probable IFI, based on standardized diagnostic criteria (15) when possible, incidence of invasive *Aspergillus* infection, and incidence of invasive *Candida* infection. Other outcomes included all-cause and IFI-related deaths, the need for empirical therapies, withdrawal due to adverse events, and liver-related adverse events.

Data collection and quality assessment. Using a standardized data extraction form, two reviewers (Y.J.Z. and G.T.) collected data on the year of publication, study population, interventions, comparators, study design and characteristics, outcomes, and funding sources (see Table S3 in the supplemental material). Quality assessment of the included studies was performed using the Cochrane tool for assessing the risk of bias (14). The six domains assessed were sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete data, and selective reporting. We also considered other sources of bias, such as industry sponsorship.

Data synthesis and analysis. (i) Analytical approach. A frequentist network meta-analysis was performed using the mvmeta command (16) in Stata version 13.0 (StataCorp, College Station, TX, USA). The summary treatment effect estimates were presented as odds ratios (ORs), with 95% confidence intervals (CIs), for treatment comparisons. We estimated the ranking probabilities of being at each possible rank for all treatments and used surface under the cumulative ranking curve (SUCRA) values to provide a hierarchy of treatments.

(ii) Assessment of inconsistency. The assumption of consistency or agreement between direct and indirect sources of evidence underpins the validity of a network meta-analysis. This can be violated either in parts of the network (loops of comparisons) or in the entire network. Therefore, we assessed the agreement between the two sources of evidence by using the loop-specific approach (local test) and design-by-treatment interaction model (global test) (17).

(iii) Network meta-regression. We investigated potential sources of heterogeneity by performing meta-regression analyses of the following study characteristics: (i) procedure performed (chemotherapy or autologous or allogeneic stem cell transplantation), (ii) follow-up period ($<$100 days or $\geq$100 days), and (iii) risk of bias (presence of high risk of bias in any of the six domains).

Cost-effectiveness analysis. (i) Model structure. A two-part decision analytic model was adopted (18) and was conducted using TreeAge Pro Suite 2015 (TreeAge Software Inc., Williamstown, MA, USA). The first part of the model simulated therapy with antifungal prophylaxis by using a decision tree. The second part simulated the natural history of the primary disease over a lifetime horizon by using a Markov model (Fig. 1).

The base case was a hypothetical cohort of 40-year-old patients with AML who were undergoing induction chemotherapy or HSCT who entered the model and could develop an IFI. The analysis was conducted separately for AML patients receiving chemotherapy and undergoing HSCT. Patients were assigned the following options for antifungal prophylaxis: fluconazole, itraconazole capsule, itraconazole solution, posaconazole, or voriconazole. Patients who developed an IFI might survive or might succumb to the infection or to non-IFI-related causes. Patients who survived the antifungal prophylaxis entered into the Markov model, which projected the risk of death from the underlying disease, independent of the patients' history of infections.

The model assumptions reflected the local practice in two 1,000-bed

TABLE 1 Model input parameters

Parameter[a]	Base case	Uncertainty (range/distribution)	Source[b]
Probabilities			
Probability of IFI			
Fluconazole	0.100	0.075–0.125 (beta)	Expert opinion
Itraconazole capsule	0.135	0.048–0.328 (beta)	NMA
Itraconazole solution	0.066	0.042–0.106 (beta)	NMA
Posaconazole	0.037	0.017–0.075 (beta)	NMA
Voriconazole	0.049	0.021–0.106 (beta)	NMA
Probability of IFI-related death	0.333	0.250–0.416 (beta)	Hospital data
Probability of death from other causes	0.100	0.075–0.125 (beta)	Pooled analysis
Probability of death from primary disease 5 yr after event			
AML patients	0.650		Hospital data
HSCT patients	0.520		Hospital data
Probability of death by age group			
40–44 yr	0.009		Singapore Department of Statistics
45–49 yr	0.015		
50–54 yr	0.027		
55–59 yr	0.043		
60–64 yr	0.070		
65–69 yr	0.110		
Costs (SGD)			
Prophylaxis for AML patients			
Fluconazole	100.80	67.20–134.40	Hospital data
Itraconazole capsule	231.84	154.56–309.12	Hospital data
Itraconazole solution	1,475.64	983.76–1,967.52	Hospital data
Posaconazole	3,397.59	2,365.06–4,430.12	Hospital data
Voriconazole	10,071.6	6,749.40–133,933.80	Hospital data
Prophylaxis for HSCT patients			
Fluconazole	134.40	134.40–403.20	Hospital data
Itraconazole capsule	309.12	309.12–927.36	Hospital data
Itraconazole solution	1,967.52	1,967.52–5,902.56	Hospital data
Posaconazole	4,430.12	4,430.12–12,690.36	Hospital data
Voriconazole	13,393.80	13,393.80–39,971.40	Hospital data
Treatment of IFI			
IA infection	41,348.35	34,703.95–47,992.75	Hospital data
IA infection, with voriconazole prophylaxis	100,293.48	83,577.90–117,009.06	Hospital data
IC infection	4,893.15	4,893.15–7,176.62	Hospital data
Laboratory investigations			
AML patients	609.40	483.30–735.50	Hospital data
HSCT patients	735.50	609.40–987.70	Hospital data
IFI	2,992.00	2,786.00–3,198.00	Hospital data
Hospitalization[c]	5,992.00	2,996.00–8,988.00	Hospital data
Outpatient visits			
AML patients	651.94	564.20–739.68	Hospital data
HSCT patients	827.42	739.68–915.16	Hospital data

[a] IFI, invasive fungal infection; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; IA, invasive *Aspergillus*; IC, invasive *Candida*.
[b] NMA, network meta-analysis.
[c] Including a 2-week hospital stay for patients with IFIs.

national and regional transplant centers in Singapore. AML patients undergoing induction chemotherapy or HSCT received 3 and 4 weeks of antifungal prophylaxis, respectively. Patients who developed invasive *Aspergillus* infections were treated with voriconazole for 12 weeks. Patients receiving voriconazole prophylaxis were treated with liposomal amphotericin B. Patients who developed invasive *Candida* infections were treated with an echinocandin (e.g., anidulafungin) for 2 weeks.

(ii) Model inputs. Transition probabilities between health states, specifically the risks of developing an IFI during prophylaxis, were derived from estimates generated by the network meta-analysis (Table 1). The respective probabilities for comparator arms (p_x) were derived using the formulas $p_x = \text{odds}_x/(1 + \text{odds}_x)$ and $\text{odds}_x = \text{OR}_{x,\text{flu}} \cdot p_{\text{flu}}/(1 - p_{\text{flu}})$, where p_{flu} is the probability of IFI for fluconazole, $\text{OR}_{x,\text{flu}}$ is the odds ratio for developing IFI for each triazole versus fluconazole as estimated in the network meta-analysis, and odds_x is the odds of each triazole leading to IFI.

The probability of death due to IFI was derived from the archives of one of the aforementioned national transplant centers. The probability of death due to other causes was generated from pooled analysis of RCTs included in the network meta-analysis. Survival beyond the prophylaxis period was derived from local hospital and epidemiological data (19). Together with the baseline probabilities of all-cause death for the Singaporean population, the 5-year overall survival rates for AML patients undergoing chemotherapy or HSCT were adjusted as the cohort aged over the time horizon of the analysis.

The analysis was conducted from the patient perspective, given that health care costs are borne by the patient in most cases. Direct medical

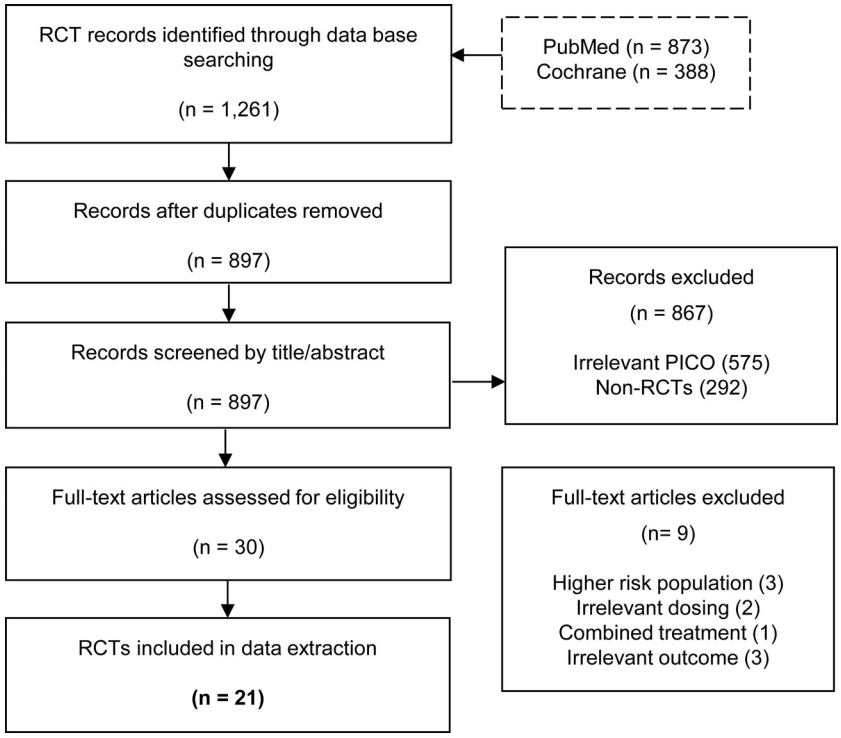


FIG 2 Study flow diagram. PICO, patient or population, intervention, comparison, or outcome(s).

costs were derived from charges in the Singapore public health care institution. The costs associated with prophylaxis include drugs and laboratory investigations. The costs of IFI treatment include drugs, investigations, hospitalization, and physician consultation fees. The laboratory and radiological investigations include the following: full blood count, analysis of serum electrolyte and creatinine levels, liver function tests, chest X-rays, computed tomographic scans, bronchoalveolar lavage fluid cultures for bacteria and fungi, blood cultures for bacteria and fungi, urinalysis and urine culture, determination of *Aspergillus* galactomannan antigen index, and measurements of serum posaconazole and voriconazole levels, where applicable. Costs were not discounted, given that the time horizon of the decision tree was less than 1 year and it was assumed that no additional costs would be incurred at posttrial follow-up assessments. Costs were calculated in 2015 Singapore dollars (SGD) (1 SGD = 0.7560 USD in May 2015) (http://www.marketwatch.com/investing/currencies/tools).

(iii) Model outcomes. The outcomes of interest were lifetime costs, episodes of IFIs avoided, and life-years (LY) saved. The additional costs associated with each successful outcome were calculated and presented as the incremental cost-effectiveness ratio (ICER).

(iv) Sensitivity analyses. Deterministic sensitivity analyses were performed to examine the effects of varying the parameters on the ICERs and to determine which parameters were the key drivers of the results. Probabilistic sensitivity analyses, using 1,000 Monte Carlo iterations, were performed to evaluate how the simultaneous uncertainties about model inputs might influence outcomes. The results were presented as a cost-effectiveness acceptability curve that indicated the probability of each antifungal agent being cost-effective over a range of willingness-to-pay (WTP) thresholds (i.e., the price that the payer finds acceptable).

RESULTS

Characteristics of included studies and patients. The electronic database search retrieved 1,261 records, of which 21 RCTs (12, 20–39) met our study inclusion criteria (Fig. 2). The studies were published between 1992 and 2013, and 14 of them (67%) were industry sponsored. The association among the five triazole antifungals, in terms of direct evidence, is presented in Fig. 3. Fluconazole was the most extensively studied.

A total of 5,505 participants were included in the review. The mean age of the study subjects was 43 years, and 58% of them were male. The median durations of antifungal prophylaxis and follow-up monitoring were 70 days and 100 days, respectively. Sixty-one percent and 39% of the patients received chemotherapy and underwent HSCT, respectively. The most common underlying disease was AML (56%). Overall, proven or probable IFIs oc-

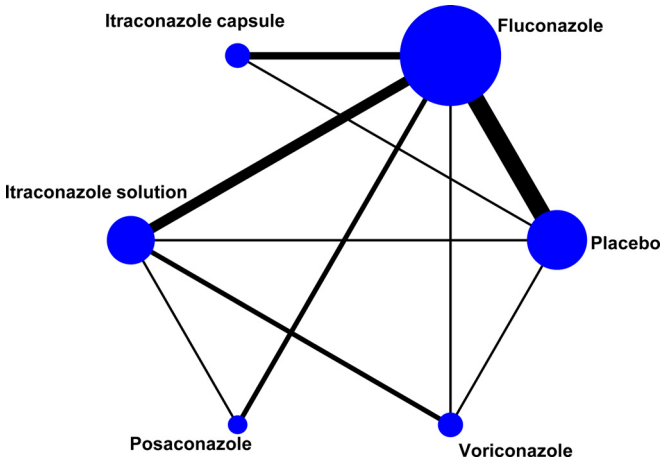


FIG 3 Network of all direct comparisons between triazole antifungal agents. The sizes of the nodes indicate the numbers of participants, and the widths of the lines indicate the numbers of included trials.

curred in 5% of the study population, with 45% and 49% being caused by *Candida* and *Aspergillus*, respectively.

The studies were generally considered to be of moderate quality. Most of the trials did not provide details about randomization procedures and allocation concealment. Only 10 and three studies had adequate randomization and allocation concealment, respectively. Eleven studies were double blind, and nine of them confirmed the success of blinding. Most of the studies followed intention-to-treat analysis, and dropouts were balanced between the treatment groups. Two-thirds of the trials were considered to be at risk of other biases because they were industry sponsored.

Network meta-analysis. (i) Overall incidences of IFIs, invasive *Aspergillus* infections, and invasive *Candida* infections. Of the 21 included studies, 20 reported outcomes of the overall incidence of IFIs (12, 20–34, 36–39) and 16 invasive *Aspergillus* infections and invasive *Candida* infections (12, 21–23, 25–32, 34, 36–38). All triazole antifungal prophylaxes except itraconazole capsule were significantly better than placebo in reducing IFIs (Fig. 4a). Posaconazole was significantly better than fluconazole (OR, 0.35 [95% CI, 0.16 to 0.73]) and itraconazole capsule (OR, 0.25 [95% CI, 0.06 to 0.97]), but not voriconazole (OR, 1.31 [95% CI, 0.43 to 4.01]), in preventing IFIs. Voriconazole was found to be more effective than fluconazole and itraconazole (capsule and solution) in reducing IFIs, but the difference did not reach statistical significance.

Posaconazole was significantly more effective than placebo (OR, 0.12 [95% CI, 0.02 to 0.61]), fluconazole (OR, 0.07 [95% CI, 0.01 to 0.29]), itraconazole solution (OR, 0.10 [95% CI, 0.02 to 0.47]), and voriconazole (OR, 6.46 [95% CI, 1.22 to 34.04]) in preventing invasive *Aspergillus* infections (Fig. 4b). However, the treatment effects of posaconazole versus voriconazole, which were generated through indirect evidence, ought to be interpreted with caution. Voriconazole was significantly better in reducing invasive *Aspergillus* infections than was fluconazole (OR, 0.42 [95% CI, 0.20 to 0.90]). Apart from itraconazole capsule, all triazole antifungals were significantly better than placebo in preventing invasive *Candida* infections (Fig. 4b). There was no significant difference among the triazole antifungals in outcomes with respect to invasive *Candida* infections.

(ii) All-cause and IFI-related deaths. We analyzed 19 and 14 studies that reported overall mortality rates at 100 days (12, 20–23, 25–38) and mortality rates related to IFIs (12, 20–23, 26–32, 34, 38), respectively. Posaconazole was associated with significant reductions in all-cause mortality rates, compared to placebo (OR, 0.49 [95% CI, 0.28 to 0.85]), fluconazole (OR, 0.54 [95% CI, 0.33 to 0.88]), and itraconazole solution (OR, 0.49 [95% CI, 0.28 to 0.83]) (Fig. 4c). Fluconazole (OR, 0.50 [95% CI, 0.28 to 0.88]), itraconazole solution (OR, 0.33 [95% CI, 0.16 to 0.70]), and posaconazole (OR, 0.14 [95% CI, 0.04 to 0.43]) were found to be significantly superior to placebo in reducing IFI-related mortality rates (Fig. 4c). Specifically for deaths attributable to IFIs, posaconazole was more beneficial than fluconazole (OR, 0.27 [95% CI, 0.10 to 0.76]) but not other agents. Although significance was not reached, the general trend was suggestive of risk reduction for both all-cause and IFI-attributable deaths in favor of voriconazole over other triazole antifungals. For both measures, the treatment effects for posaconazole versus voriconazole were not statistically significant.

(iii) Empirical therapies. We analyzed 15 studies that reflected the use of empirical therapies (20, 21, 23, 25–33, 35–37). With the exception of itraconazole capsule, the use of triazole antifungal prophylaxis resulted in significantly fewer patients requiring initiation of empirical antifungal therapies, compared to placebo (Fig. 4d). Specifically, fewer patients receiving posaconazole prophylaxis required empirical therapies, compared with fluconazole (OR, 0.35 [95% CI, 0.15 to 0.80]), itraconazole capsule (OR, 0.33 [95% CI, 0.12 to 0.95]), and itraconazole solution (OR, 0.37 [95% CI, 0.15 to 0.91]). Voriconazole also led to significantly fewer patients receiving empirical therapies, compared to fluconazole (OR, 0.66 [95% CI, 0.45 to 0.96]).

(iv) Ranking. We generated hierarchies of treatment effects on the basis of SUCRA values for prophylaxis against IFIs. A value of 1 indicates that a treatment is certain to be the best, and a value of 0 indicates that it is certain to be the worst. The SUCRA values for the five treatments were as follows: posaconazole, 0.92; voriconazole, 0.80; itraconazole solution, 0.63; fluconazole, 0.36; itraconazole capsule, 0.27.

(v) Tolerability. Itraconazole solution was associated with a significantly higher rate of withdrawal due to adverse events, in comparison with fluconazole (OR, 1.84 [95% CI, 1.11 to 3.06]) (Fig. 5a). Against placebo, all triazole antifungals had comparable rates of withdrawal due to adverse events. No other significant differences in rates of withdrawal due to adverse events were detected among the triazole antifungals.

Treatment-related liver function abnormalities occurred more frequently with voriconazole than with fluconazole (OR, 3.63 [95% CI, 1.90 to 6.93]), itraconazole solution (OR, 2.34 [95% CI, 1.32 to 4.13]), and placebo (OR, 3.61 [95% CI, 1.78 to 7.36]) (Fig. 5b). Itraconazole solution was associated with more patients having liver function abnormalities, compared to fluconazole (OR, 1.55 [95% CI, 1.11 to 2.18]).

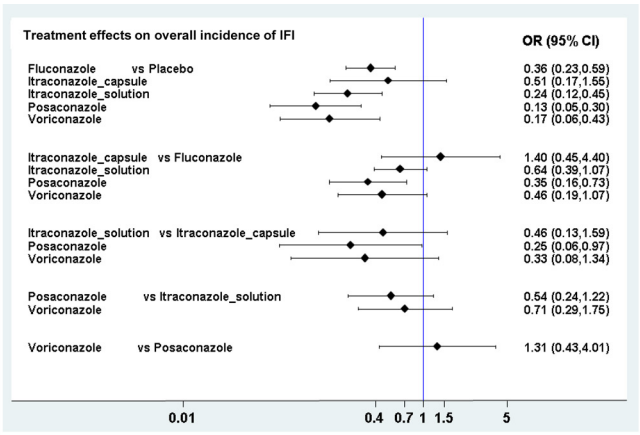
(vi) Assessment of inconsistency. Loop-specific tests did not detect any statistical inconsistency. For one of the four closed loops identified (i.e., placebo-fluconazole-itraconazole solution), however, the confidence interval was wide. The wide spread could be due to two studies (by Chandrasekar and Gatny [21] and Schaffner and Schaffner [32]) in the loop that reported slightly worse effects for fluconazole prophylaxis versus placebo (overall incidences of IFIs of 2/23 subjects versus 1/23 subjects and 8/75 subjects versus 8/76 subjects, respectively), while other studies reported findings that favored fluconazole. The results and conclusion regarding the overall incidence of IFIs remained the same after the exclusion of those two trials from the primary analysis. Based on a design-treatment interaction model, no significant inconsistency between direct and indirect evidence was identified within the evidence network as a whole ($P > 0.05$).

(vii) Network meta-regression. Meta-regression analyses showed that efficacy, in terms of the overall incidence of IFIs, did not differ with respect to procedures performed, length of the follow-up period, and trial-specific risk of bias ($P > 0.05$).

Cost-effectiveness analysis. (i) Base-case analysis. The outcomes and total costs accrued over a lifetime horizon in two different cohorts, i.e., AML and HSCT patients, are shown in Tables 2 and 3, respectively. The ICERs were calculated relative to fluconazole, which was considered the standard of care. Prophylaxes with itraconazole solution and fluconazole were associated with the lowest costs in the AML and HSCT groups, respectively.

In both cohorts, posaconazole was associated with the greatest benefits in terms of numbers of IFIs avoided and LY saved. In contrast, itraconazole capsule was dominated by fluconazole and

a)



b)

Placebo	1.77 (0.85,3.71)	0.51 (0.02,15.28)	1.11 (0.47,2.62)	**0.12 (0.02,0.61)**	0.75 (0.26,2.14)
0.14 (0.08,0.25)	Fluconazole	0.29 (0.01,9.34)	0.62 (0.37,1.04)	**0.07 (0.01,0.29)**	**0.42 (0.20,0.90)**
0.33 (0.06,1.66)	2.35 (0.42,13.17)	Itraconazole capsule	2.18 (0.06,73.14)	0.23 (0.01,10.05)	1.47 (0.04,51.97)
0.08 (0.03,0.20)	0.58 (0.26,1.28)	0.25 (0.04,1.60)	Itraconazole solution	**0.10 (0.02,0.47)**	0.67 (0.28,1.61)
0.20 (0.05,0.78)	1.47 (0.43,4.98)	0.62 (0.08,5.15)	2.54 (0.64,10.16)	Posaconazole	**6.46 (1.22,34.04)**
0.09 (0.02,0.34)	0.64 (0.18,2.20)	0.27 (0.03,2.25)	1.10 (0.29,4.23)	0.43 (0.08,2.43)	Voriconazole

Invasive *Candida* infection Invasive *Aspergillus* infection

c)

Placebo	0.90 (0.68,1.20)	1.08 (0.41,2.85)	1.00 (0.69,1.45)	**0.49 (0.28,0.85)**	0.76 (0.48,1.19)
0.50 (0.28,0.88)	Fluconazole	1.21 (0.45,3.25)	1.11 (0.84,1.47)	**0.54 (0.33,0.88)**	0.84 (0.58,1.22)
1.36 (0.17,10.73)	2.74 (0.33,22.45)	Itraconazole capsule	0.92 (0.33,2.56)	0.45 (0.15,1.35)	0.70 (0.24,2.01)
0.33 (0.16,0.70)	0.67 (0.40,1.13)	0.25 (0.03,2.13)	Itraconazole solution	**0.49 (0.28,0.83)**	0.76 (0.53,1.09)
0.14 (0.04,0.43)	**0.27 (0.10,0.76)**	0.10 (0.01,1.03)	0.40 (0.13,1.21)	Posaconazole	1.56 (0.86,2.84)
0.12 (0.00,3.97)	0.24 (0.01,7.70)	0.09 (0.00,5.05)	0.36 (0.01,10.98)	0.89 (0.02,32.23)	Voriconazole

Mortality attributable to IFI All-cause mortality

d)

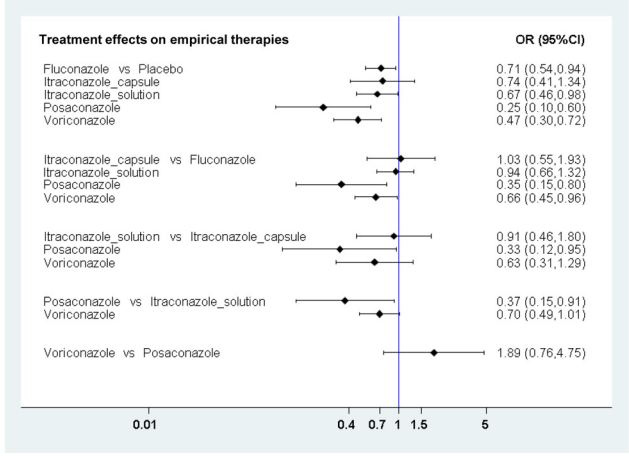


FIG 4 Treatment effects on the overall incidence of proven or probable invasive fungal infections (IFIs) (a), invasive *Aspergillus* infections and invasive *Candida* infections (b), all-cause deaths and deaths attributable to IFIs (c), and the need for empirical therapies (d). (a and d) Forest plots depicting the treatment effects on proven or probable IFIs (a) and the need for empirical therapies (d), presented as odds ratios (ORs) with 95% confidence intervals (CIs). (b) Effects of

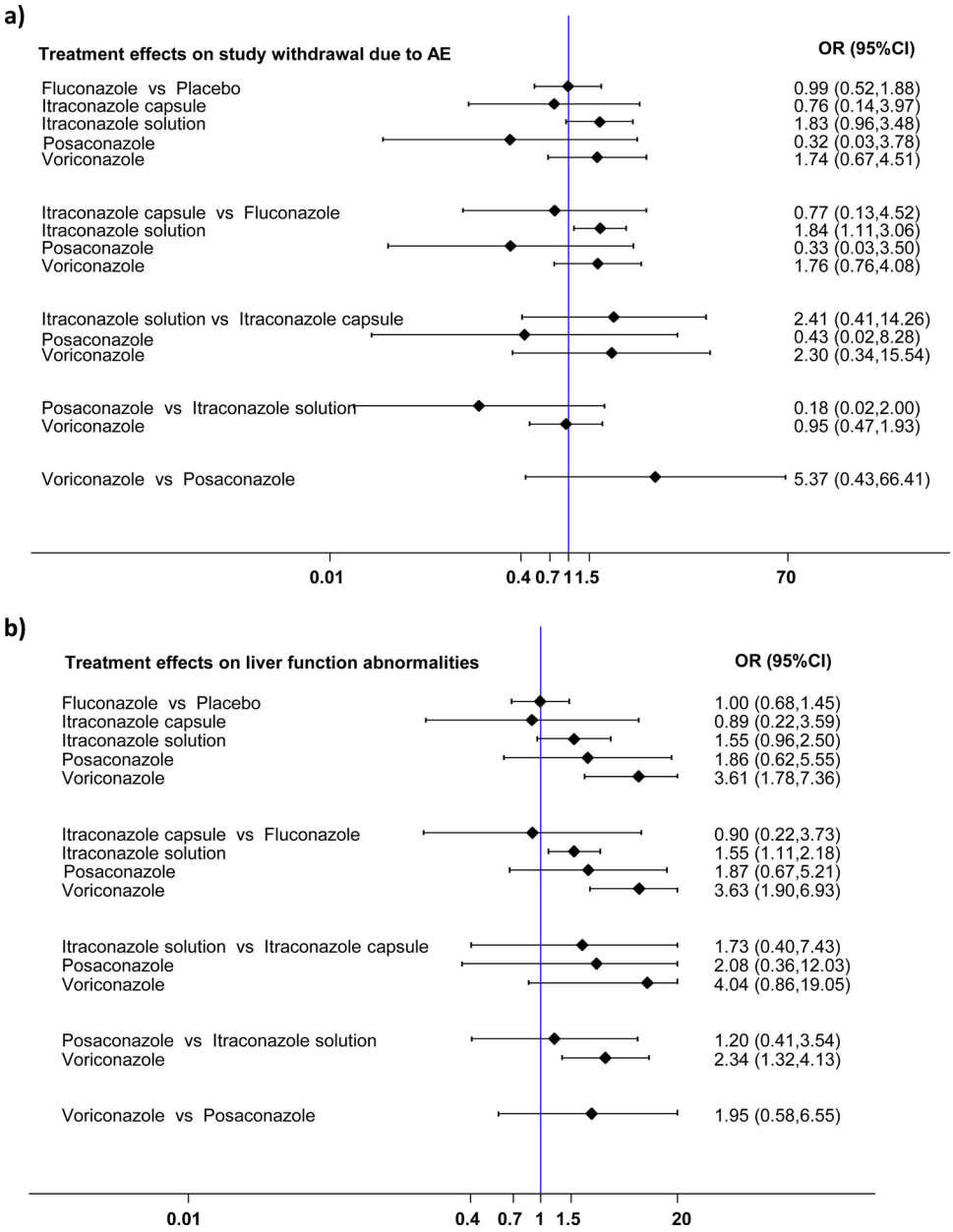


FIG 5 Treatment effects on study withdrawal due to adverse events (AE) (a) and liver function abnormalities (b). The Forest plots depict the treatment effects presented as odds ratios (ORs) with 95% confidence intervals (CIs).

the other treatments, i.e., comparatively more costly and less effective than the other triazole antifungal agents (highest incidence of IFIs and lowest LY saved). Compared to fluconazole, itraconazole solution, posaconazole, and voriconazole were all associated with fewer IFIs per patient (0.034, 0.063, and 0.051 episodes avoided, respectively) and increased LY over a lifetime horizon.

Itraconazole solution dominated fluconazole in the AML cohort, i.e., comparatively less costly and more effective than fluconazole. In the HSCT cohort, the ICERs for itraconazole solution were SGD 12,546 per IFI avoided and SGD 5,844 per LY saved. Posaconazole and voriconazole were associated with greater efficacy than itraconazole solution but at higher costs.

treatments on invasive *Aspergillus* infections (upper) and invasive *Candida* infections (lower). Comparisons between treatments should be read from left to right; the OR (with 95% CI) in each cell is the comparison between the column-defined treatment and the row-defined treatment. ORs of <1 favor the row-defined treatment (lower) or the column-defined treatment (upper). Significant results are shown in bold. (c) Effects of treatments on all-cause deaths (upper) and deaths attributable to invasive fungal infections (lower). Comparisons between treatments should be read from left to right; the OR (with 95% CI) in each cell is the comparison between the column-defined treatment and the row-defined treatment. ORs of <1 favor the row-defined treatment (lower) or the column-defined treatment (upper). Significant results are shown in bold.

TABLE 2 Costs and health outcomes for AML patients

Treatment	Total cost (SGD)	Effectiveness[a]				ICER	
		No. of IFIs	No. of IFIs avoided	LY	LY saved	Per IFI avoided	Per LY saved
Fluconazole	4,186.91	0.100		5.197			
Itraconazole capsule	5,748.09	0.135	−0.035	5.134	−0.063	Dominated	Dominated
Itraconazole solution	4,172.47	0.066	0.034	5.258	0.061	Dominant	Dominant
Posaconazole	4,909.45	0.037	0.063	5.310	0.113	11,469	6,394
Voriconazole	14,095.61	0.049	0.051	5.288	0.091	194,288	108,887

[a] IFI, invasive fungal infection; LY, life-years; ICER, incremental cost-effectiveness ratio.

The indicative ICERs reported were calculated relative to fluconazole. In the AML cohort, the ICERs for posaconazole were SGD 11,469 per IFI avoided and SGD 6,394 per LY saved. In the HSCT cohort, the ICERs for posaconazole were SGD 26,817 per IFI avoided and SGD 12,423 per LY saved. Comparatively, the ICERs for voriconazole were higher, ranging from SGD 108,887 to SGD 258,263. Hence, voriconazole was dominated by posaconazole in both the AML and HSCT cohorts.

(ii) Sensitivity analysis. Deterministic sensitivity analyses revealed that the results were most sensitive to the probabilities of IFIs associated with itraconazole solution and posaconazole. However, those values did not have any discernible impact on the primary analyses. The probability of each triazole antifungal being cost-effective was analyzed and presented for different WTP thresholds. Probabilistic sensitivity analyses showed that, at lower WTP thresholds, itraconazole solution had a higher probability of being cost-effective than did posaconazole (Fig. 6a and b). Beyond WTP thresholds of SGD 15,000 and SGD 25,000 per LY saved, however, the probabilities of being cost-effective for posaconazole were higher than those for itraconazole solution in the AML and HSCT cohorts, respectively.

DISCUSSION

In this comparative analysis of all triazoles used in clinical practice, we evaluated their efficacy, tolerability, and cost-effectiveness as prophylaxis against IFIs. Overall, posaconazole was superior in reducing IFIs and all-cause deaths among patients receiving chemotherapy or undergoing HSCT. In the context of relative cost-effectiveness, itraconazole solution was least costly, particularly as prophylaxis in the AML cohort. The ICER for posaconazole was higher than that for itraconazole solution.

Traditional meta-analysis of direct comparisons becomes limited when there is no clinical study assessing a particular pair of agents (for example, posaconazole versus voriconazole). The advanced quantitative technique of network meta-analysis provides the means of generating treatment effects in such instances, by incorporating both direct and indirect comparisons, and increasingly is being used to guide the choice of therapy. By integrating results from the network meta-analysis, we were able to compare the cost-effectiveness among all four agents using efficacy data from RCTs. In recent years, pharmacoeconomic evaluations of the newer triazoles have been reported, in view of their greater drug acquisition costs. To our current knowledge, however, there has been no cost-effectiveness analysis (CEA) involving the simultaneous evaluation of fluconazole, itraconazole capsule and oral solution, posaconazole, and voriconazole. Hence, our study provided novel insights through a comprehensive overview of the cost-effectiveness of all of the triazole antifungals currently in use.

We evaluated the relative cost-effectiveness of the agents based on their ICERs, using fluconazole as a common comparator. This is in line with current clinical practice, where fluconazole has been the standard of care. Earlier models (9, 18) lacked the ability to compare posaconazole and itraconazole independently. To overcome this, we derived effect estimates from studies involving itraconazole other than that by Cornely et al. (12). This increased the precision of the estimate of relative efficacy between two treatments, by coupling direct and indirect comparisons. While it appeared that itraconazole solution may offer the best value in specific situations, it should be noted that other factors should also be taken into consideration. Itraconazole solution was associated with a significantly higher rate of study withdrawal than were other triazole antifungals. This could be the result of the higher incidence of gastrointestinal side effects caused by the cyclodextrin vehicle used in the formulation. Therefore, tolerability and drug adherence, and in turn effectiveness in practice, become questionable.

The analysis of comparative efficacy among all of the triazole antifungals was in favor of posaconazole, based on the various outcomes. In addition, the efficacy hierarchy generated by our analysis was indicative of posaconazole being most efficacious for prophylaxis against IFIs, followed by voriconazole and itraconazole solution. Although our network meta-analysis included a recent RCT evaluating posaconazole among 117 patients with chemotherapy-induced neutropenia (33), which was not covered in a

TABLE 3 Costs and health outcomes for HSCT patients

Treatment	Total cost (SGD)	Effectiveness[a]				ICER	
		No. of IFIs	No. of IFIs avoided	LY	LY saved	Per IFI avoided	Per LY saved
Fluconazole	4,271.27	0.100		6.247			
Itraconazole capsule	5,893.90	0.135	−0.035	6.172	−0.075	Dominated	Dominated
Itraconazole solution	4,697.85	0.066	0.034	6.320	0.073	12,546	5,844
Posaconazole	5,960.76	0.037	0.063	6.383	0.136	26,817	12,423
Voriconazole	17,442.68	0.049	0.051	6.357	0.110	258,263	119,740

[a] IFI, invasive fungal infection; LY, life-years; ICER, incremental cost-effectiveness ratio.

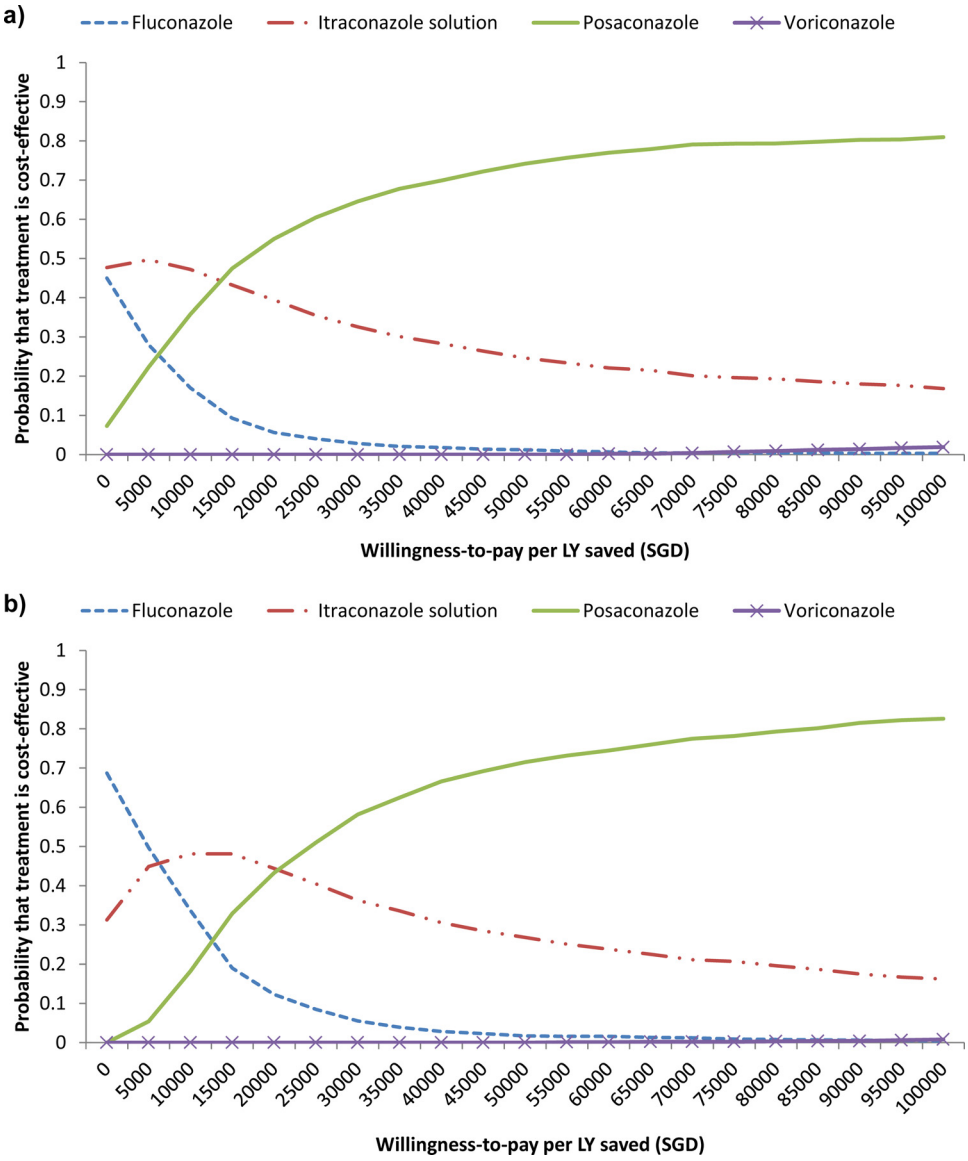


FIG 6 Cost-effectiveness acceptability curves for AML (a) and HSCT (b) cohorts. LY, life-year.

prior analysis (40), a clear difference in efficacy between posaconazole and voriconazole was not seen.

In two other pharmacoeconomic evaluations that compared posaconazole and voriconazole, the efficacy and cost data were captured retrospectively from a cohort of AML patients (8, 13). Their analysis may be limited in terms of the robustness of data from a cohort study, as opposed to a RCT, as well as the sample size. Our results corroborated the results from a previous analysis that indicated that posaconazole was more cost-beneficial than voriconazole for AML patients undergoing chemotherapy (8). Similarly, compared to narrow-spectrum triazole antifungals, posaconazole and voriconazole appeared less cost-effective than fluconazole in AML patients undergoing consolidation chemotherapy (13).

The WTP threshold has not been officially defined in Singapore, although the general consensus is to be set at 1 gross domestic product (GDP) per capita, which in 2014 was SGD 70,000 (US$52,920) per quality-adjusted life-year (QALY) gained. Given that our outcomes were episodes of IFI avoided and LY saved, rather than QALY, the applicability of the WTP threshold becomes limited. The costs associated with IFI treatment may be taken into account in the interpretation of ICERs; in a local case-matched cohort study involving 66 cases in two major oncology centers, these costs were reported as SGD 39,000 (US$29,484) (L. Hsu, S. Teng, X. Zhang, Y. Xie, V. Pawar, and B. H. Tan, presented at the 13th Asia-Pacific Congress of Clinical Microbiology and Infection, Beijing, China, 2012). The ICERs for itraconazole solution and posaconazole (range, SGD 11,469 to 26,817 per IFI avoided) may be viewed as indicating that these two agents were cost-effective in the setting of the Singapore health care system.

Our findings cannot be generalized to other patient cohorts with different IFI risks, such as patients with GVHD, who were excluded from the evidence network reported here. No distinction was made in our analysis between patients who received chemo-

therapy versus HSCT, due to data availability. When we performed a meta-regression analysis of data for these two groups of patients, the overall incidence of IFIs did not differ significantly according to the procedure performed. As with any systematic review, there are intrinsic biases that may influence the results. Potential bias could arise from study heterogeneity, such as in study populations (age and severity of illness) and study designs (duration of prophylaxis and follow-up monitoring). To this end, we performed network meta-regression and found that these factors had no significant impact on our results. The risk of publication bias having an effect on our results cannot be ruled out, given that only English-language articles and studies with fully published results were considered for inclusion. In antifungal prophylaxis trials, there is a possibility of informative censoring when participants prematurely leave the study for various reasons, which inevitably affects the rate of IFIs, a common endpoint in most cases. To alleviate this concern, Wingard et al. attempted an unconventional study design by adopting fungus-free survival (FFS) (i.e., alive and free of proven, probable, or presumptive IFI at 180 days) as the endpoint, rather than the overall incidence of IFIs (36). However, the paucity of such studies limited our ability to include this outcome in the current analysis. In addition to the primary outcome (i.e., incidence of IFIs), we analyzed the study dropout rates and the rates of deaths due to IFI and non-IFI-related causes, in an attempt to address informative censoring. In the cost-effectiveness analysis, we assumed that the long-term survival of a patient was independent of the history of IFI and that no additional costs pertaining to IFI management were incurred in the postprophylaxis period. While that may lead to consistent underestimation of the long-term costs across treatments, it would not affect the relative cost-effectiveness among the comparators.

The output from this comparative efficacy and cost-effectiveness study seeks to provide a framework for holistic decisions regarding appropriate antifungal agents, with due consideration of available health care resources. It remains to be highlighted that decisions regarding antifungal prophylaxis at the bedside invariably must weigh patient-specific factors such as individual susceptibility to adverse effects and drug interactions, such as avoidance of specific azoles during exposure to cyclophosphamide or vincristine. The capacity of the patient for enteral assimilation is also critical. For patients with a history of congestive heart failure, poorly controlled hypertension, or hepatic dysfunction, clinicians may choose to be cautious with itraconazole and voriconazole.

Our analysis showed that antifungal prophylaxis with triazoles (with the exception of itraconazole capsule) reduced IFI rates and increased survival rates in patients. Posaconazole was superior in reducing IFIs and all-cause deaths, compared to most triazole antifungals, and was considered cost-effective. Itraconazole solution might be a viable and cost-effective option specifically for AML patients; however, this must be weighed against the efficacy and tolerability of itraconazole solution.

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